IN THE UNITED STATES DISTRICT COURT
DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

Palmetto Pharmaceuticals LLC, Plaintiff, v. AstraZeneca Pharmaceuticals LP, Defendant.	C/A No. 2:11-cv-00807-SB **CLAIM CONSTRUCTION REPORT AND RECOMMENDATION**

Whereas, pursuant to Rule 53 of the Federal Rules of Civil Procedure, the parties have consented to the appointment of Special Master Julian W. Dority for the purpose of assisting the Court with the *Markman* hearing and the claim construction order. Special Master Julian W. Dority has reviewed the evidence of record and considered the briefs presented by the parties in conjunction with the arguments presented during the *Markman* hearing conducted on January 13, 2015. Pursuant to *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996), Special Master Julian W. Dority now construes the claim terms at issue.

BACKGROUND

U.S. Patent No. 6,465,516 B1 (the "'516 Patent"), entitled "Method of Stimulating Nitric Oxide Synthase," was issued on October 15, 2002. The '516 Patent is a continuation of patent application number 08/833,842, which was filed on April 10, 1997 and issued as U.S. Patent No. 5,968,983 (the "'983 Patent") on October 19, 1999.

A request for an Ex Parte Reexamination of the '516 Patent was filed on March 26, 2010, and an Ex Parte Reexamination Certification was issued on April 5, 2011 as 6,465,516 C1 (the "Reexamined '516 Patent"). During reexamination, the United States Patent and Trademark Office found that original claims 1 and 3-6 of the '516 Patent were patentable (as amended) and

that original claims 7-14 and new claims 5-20 were also patentable; original claim 2 was cancelled. Reexamined '516 Patent col.1 ll.17-26.

Palmetto Pharmaceuticals LLC ("Palmetto") filed this infringement action on April 5, 2011 and alleges that "AstraZeneca Pharmaceuticals makes, offers to sell and sells a Hmg-CoA reductase inhibitor called Crestor (rosuvastatin calcium)." Am. Compl. at 11 ¶ 43, ECF No. 27.[1] Palmetto alleges that AstraZeneca Pharmaceuticals LP ("AstraZeneca") infringes the claims of the Reexamined '516 Patent via direct infringement, induced infringement, and contributory infringement. *Id.* at 13-15.

The matter currently before the Court is the construction of certain claim terms in the '516 Patent and the Reexamined '516 Patent. The following is a representative claim of the Reexamined '516 Patent:

> 1. A method for treating a nonhyperlipidemic subject who would benefit from increased Nitric Oxide production in a tissue comprising:
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> administering to the nonhyperlipidemic subject in need of such treatment a Hmg-CoA reductase inhibitor in an amount effective to increase Nitric Oxide production in said tissue of the subject.

Reexamined '516 Patent col.1 l.28-col.2 l.5.

AstraZeneca contends that some of the claim terms are indefinite while the parties are in dispute regarding the proper construction of other claim terms. In addition, AstraZeneca asserts that amendments presented during reexamination of the '516 Patent constitute an improper broadening of the claim scope.

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[1] Unless otherwise noted, the Special Master cites to docket entries in *Palmetto Pharm. LLC v. AstraZeneca Pharm. LP*, Case No. 2:11-cv-00807-SB.

LEGAL STANDARDS

A. Claim Construction

Claim construction is a matter of law. *See Markman*, 517 U.S. at 384; *see also Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 574 U.S. __, 135 S. Ct. 831, 834 (2015) ("[t]he ultimate construction of the claim is a legal conclusion"). "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)) (internal quotation marks omitted). The Supreme Court has stated that "the claims are 'of primary importance, in the effort to ascertain precisely what it is that is patented.' " *Phillips*, 415 F.3d at 1312 (quoting *Merrill v. Yeomans*, 94 U.S. 568, 570 (1876)).

To determine the meaning of the claims, courts start by considering the intrinsic evidence. *See Phillips*, 415 F.3d at 1313. The most "significant source of the legally operative meaning of disputed claim language" is the intrinsic evidence of record, that is, the claims, the specification, and the prosecution history. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). This is because "the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Phillips*, 415 F.3d at 1313; *see also DeMarini Sports, Inc. v. Worth, Inc.*, 239 F.3d 1314, 1324 (Fed. Cir. 2001) ("We cannot look at the ordinary meaning of [a] term . . . in a vacuum. Rather, we must look at the ordinary meaning in the context of the written description and the prosecution history . . . to determine the proper construction of that term . . . .").

Generally, claim terms are given the ordinary and customary meaning that would be ascribed to them by a person of ordinary skill in the field of the invention. *Phillips*, 415 F.3d at 1312-13; *see also Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed. Cir. 2001) (citations omitted) ("[U]nless compelled to do otherwise, a court will give a claim term the full range of its ordinary meaning as understood by an artisan of ordinary skill."). Thus, "[t]he inventor's words that are used to describe the invention-the inventor's lexicography-must be understood and interpreted by the court as they would be understood and interpreted by a person in that field of technology." *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed. Cir. 1998); *see also ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003) (citations omitted) ("[T]he context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms.").

In some cases, the specification may reveal a "special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such instances, "the inventor's lexicography governs." *Phillips*, 1415 F.3d at 1316. "Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001). "The patentee may demonstrate intent to deviate from the ordinary and accustomed meaning of a claim term by including in the specification expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002) (citing *SciMed*, 242 F.3d at 1344).

While claims are to be construed in light of the specification, courts must be careful not to read limitations from the specification into the claim. *See Phillips*, 415 F.3d at 1323. For example, if a patent specification describes only a single embodiment of a claimed invention, that does not mean that the claims of the patent necessarily must be construed as limited to that embodiment. *See id.* Rather, the purpose of the specification is "to teach and enable those of skill in the art to make and use the invention and to provide a best mode for doing so." *Id.* (citing *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1987)).

When the intrinsic evidence, that is the claims, the specification, and the prosecution history, unambiguously describes the scope of a patented invention, reliance on extrinsic evidence, which is everything outside the intrinsic evidence, is improper. *See Vitronics*, 90 F.3d at 1583. Generally, the "extrinsic evidence . . . is less significant than the intrinsic record in determining the legally operative meaning of claim language." *Phillips*, 415 F.3d at 1317 (citations omitted) (internal quotation marks omitted). While the Court may consult extrinsic evidence to educate itself about the invention and relevant technology, it may not rely upon extrinsic evidence to reach a claim construction that is clearly at odds with a construction mandated by the intrinsic evidence. *See Key Pharm. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998); *see also Markman*, 52 F.3d at 981 (Extrinsic evidence may not be used "for the purpose of varying or contradicting the terms in the claims.").

B. Indefiniteness

A patent specification must "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as [the] invention." 35

U.S.C. § 112, ¶ 2 (2006).[2] "[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S.Ct. 2120, 2124 (2014). However, "some modicum of uncertainty is the 'the price of ensuring the appropriate incentives for innovation.' " *Nautilus*, 134 S.Ct. at 2123 (quoting *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 732 (2002)). "One must bear in mind, moreover, that patents are 'not addressed to lawyers, or even to the public generally,' but rather to those skilled in the relevant art." *Id.* (quoting *Carnegie Steel Co. v. Cambria Iron Co.*, 185 U.S. 403, 437 (1902)).

Indefiniteness is a question of law. *See DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1260 (Fed. Cir. 2014) (citation omitted). To the extent factual findings support a Court's indefiniteness conclusion, they must be proven by clear and convincing evidence. *See X2Y Attenuators, LLC v. Int'l Trade Comm'n*, 757 F.3d 1358, 1365 (Fed. Cir. 2014); *see also Microsoft Corp. v. i4i Ltd. P'ship*, 131 S.Ct. 2238, 2240 (2011) (stating that invalidity defenses require clear and convincing evidence).

C. Broadening During Reexamination

Whether an amendment made during reexamination enlarges the scope of a claim is a matter of claim construction. *See In re Freeman*, 30 F.3d 1459, 1464 (Fed. Cir. 1994). Under 35 U.S.C. § 305, "[n]o proposed amended or new claim enlarging the scope of a claim of the patent will be permitted in a reexamination proceeding." Claims that are impermissibly broadened during reexamination are invalid, and "a violation of 35 U.S.C. § 305 is an invalidity defense in a

[2] Section 112 was modified by the Leahy-Smith America Invents Act, enacted by Congress in 2011. However, the amended version is only applicable to patent applications filed on or after September 16, 2012. Therefore, citations to the United States Code in this report are to the 2006 edition.

patent infringement action." *Quantum Corp. v. Rodime, PLC*, 65 F.3d 1577, 1584 (Fed. Cir. 1995).

"The test for determining whether a reexamined claim is broader than an original claim under 35 U.S.C. § 305 is the same as that in 35 U.S.C. § 251, last paragraph, for determining whether reissue claims filed more than two years after issuance of the original patent are broader than the original claims." *Quantum*, 65 F.3d at 1582 n.4 (citing *Freeman*, 30 F.3d at 1464). "A claim of a reissue application is broader in scope than the original claims if it contains within its scope any conceivable" subject matter "which would not have infringed the original patent." *Tillotson, Ltd. v. Walbro Corp.*, 831 F.2d 1033, 1037 n.2 (Fed. Cir. 1987) (citations omitted); *see also Freeman*, 30 F.3d at 1464 (citing *Ex parte Newirth*, 229 U.S.P.Q. 71 (B.P.A.I. Sept. 24, 1985)) ("A claim is enlarged if it includes within its scope any subject matter that would not have infringed the original patent.").

DISCUSSION

A. Level of Ordinary Skill in the Art

Patent claims are to be construed to reflect the understanding of a person of ordinary skill in the art at the time of the invention. *See Phillips*, 415 F.3d at 1313 ("[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention . . . ."). Thus, it is important to first identify and understand the requisite level of ordinary skill in the relevant art.

Here, the parties have submitted expert declarations and reports with opinions in support of their positions. Nonetheless, the parties disagree about the relevant fields and the requisite level of skill. According to Palmetto's expert, Dr. John Hallett, "a person of ordinary skill in the art is a medical doctor or advanced clinical practitioner who treats patients with cardiovascular

conditions and has experience prescribing statins." Palmetto's Reply Br. at 12, ECF No. 379 (citation omitted). According to AstraZeneca's experts, Dr. Peter Ganz and Dr. David Harrison, "a person of ordinary skill in the art at the time of the claimed invention . . . would have at least an M.D., with a board certification in cardiology (or substantially similar field) and five years of clinical experience treating patients with cardiovascular diseases and abnormal lipid levels." AstraZeneca's Opening Br. at 13, ECF No. 367 (citations omitted).

During reexamination of the '516 Patent, the Examiner also considered the level of ordinary skill in the art at the time of the invention. The Examiner stated that "[t]he level of training of the person of skill who treats or performs medical research into cardiocerebrovascular diseases is *quite high*. The artisan would be a physician or a Ph. D. in biochemistry or related field with post-doctoral experience." '516 Reexamination File Wrapper, Office Action of Sept. 1, 2010 at 9, PALM0012612, ECF Nos. 229-242 (hereinafter "Sept. 2010 Office Action") (emphasis added).

In light of the above and as suggested by the Examiner during reexamination, the Special Master finds that a person of ordinary skill in the art would have at least an M.D., with a board certification in cardiology (or substantially similar field) and at least five years of clinical experience treating patients with cardiovascular diseases and abnormal lipid levels.

B. Claim Construction

Palmetto and AstraZeneca dispute the proper construction of certain claim terms of claim 1 of the Reexamined '516 Patent. Claim 1 is set forth below with those terms requiring a construction presented in bold:

1. **A method for treating a nonhyperlipidemic subject who would benefit from increased Nitric Oxide production in a tissue** comprising:

administering to the **nonhyperlipidemic subject in need of such treatment** a Hmg-CoA reductase inhibitor in an **amount effective** to **increase Nitric Oxide production** in said tissue of the subject.

Taking into consideration the intrinsic evidence and the extrinsic evidence of record, the Special Master construes the claim terms at issue as follows.

I. "method for treating" and "[such] treatment"

Palmetto's Proposed Construction	AstraZeneca's Proposed Construction
"administration of a Hmg-CoA reductase inhibitor"	"administration of a mixture or combination of L-arginine and a Hmg-CoA reductase inhibitor"

Palmetto asserts that the phrases "method for treating" and "[such] treatment" require the "administration of a Hmg-CoA reductase inhibitor" while AstraZeneca asserts that the phrases require the "administration of a mixture or combination of L-arginine and a Hmg-CoA reductase inhibitor."

In construing disputed claim terms, we first look to the intrinsic evidence, including the claims, the specification, and the prosecution history. *See Phillips*, 415 F.3d at 1313. Beginning with the claims, the plain language of claim 1 of the Reexamined '516 Patent simply requires "administering . . . a Hmg-CoA reductase inhibitor" and does not explicitly require the "administration of a mixture or combination of L-arginine and an Hmg-CoA reductase inhibitor." *See* Reexamined '516 Patent col.1 l.28-col.2 l.5.

The prosecution history of the '516 Patent also supports a construction in which the "administration of a mixture or combination of L-arginine and a Hmg-CoA reductase inhibitor"

is not required. The application[3] for the '516 Patent was originally filed with claim 1 requiring the following step: "administering a mixture of L-arginine and an inhibitor of Hmg-CoA reductase." '516 Patent File Wrapper, '516 Patent Application of Oct. 18, 1999 at 17, PALM0000030, ECF Nos. 229-242. However, in conjunction with the application, the '516 Patentee filed a Preliminary Amendment amending claim 1 to remove any reference to "a mixture of L-arginine" thereby providing the following step: "administering an inhibitor of Hmg-CoA reductase." '516 Patent File Wrapper, Preliminary Amendment of Oct. 18, 1999 at 2, PALM0000010, ECF Nos. 229-242. Therefore, the Special Master recognizes that, had they intended to do so, the '516 Patentee knew exactly how to draft a claim requiring "the administration of a mixture or combination of L-arginine and a Hmg-CoA reductase inhibitor." However, the Preliminary Amendment clearly demonstrates that the '516 Patentee had no such intentions.

This was even recognized by the Examiner during prosecution. Tellingly, the Examiner issued an Election Requirement and stated that the claims are directed to "Hmg-CoA reductase inhibitors, *optionally* in combination with an endothelial cell nitric oxide synthetase [sic] substrate." '516 Patent File Wrapper, Office Action of Dec. 8, 1999 at 2, PALM0000145, ECF Nos. 229-242 (emphasis added). In another Office Action, the Examiner stated that "instant claim 1 *does not require* arginine" while stating that "claim 26 is directed to administering *both* an *endothelial nitric oxide synthase substrate*, of which arginine is an example, with an *Hmg-CoA reductase inhibitor*." '516 Patent File Wrapper, Final Office Action of Jan. 30, 2002 at 4, PALM0000673, ECF Nos. 229-242 (hereinafter "Jan. 2002 Office Action") (emphases added).

[3] The application for the '516 Patent is a continuation of application number 08/833,842, which is now the '983 Patent. '516 Patent, at [63]. Unlike claim 1 of the Reexamined '516 Patent, claim 1 of the '983 Patent explicitly requires a step of "administering a mixture of L-arginine and an inhibitor of Hmg-CoA reductase." '983 Patent col.10 ll.21-23.

Not only did the Examiner acknowledge that claim 1 does not necessarily require the administration of a substrate of Nitric Oxide Synthase, such as L-arginine, the Examiner also distinguished those claims that in fact do require the administration of such a substrate.

Notwithstanding the above, AstraZeneca asserts that the claims should be construed to require the "administration of a mixture or combination of L-arginine and a Hmg-CoA reductase inhibitor" based on the premise that "[w]hen the specification's language establishes that the claims only cover a particular embodiment of the invention, the scope of the claims is limited to that embodiment." AstraZeneca's Opening Br. at 14 (citing *Honeywell Int'l, Inc. v. ITT Indus., Inc.*, 452 F.3d 1312, 1318 (Fed. Cir. 2006)).

However, "particular embodiments appearing in the written description will not be used to limit claim language that has broader effect. Even when a patent describes only a single embodiment, claims will not be 'read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction.' " *Innova*, 381 F.3d at 1117 (citation omitted); *see also Phillips*, 415 F.3d at 1323 (citing *Gemstar-TV Guide Int'l, Inc. v. Int'l Trade Comm'n*, 383 F.3d 1352, 1366 (Fed. Cir. 2004)) ("[W]e have expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment.").

In this case, there is nothing that signifies an "expression of manifest exclusion or restriction" demonstrating an intent to limit the scope of claim 1 to require the "administration of a mixture or combination of L-arginine and a Hmg-CoA reductase inhibitor." Without such a clear intention on the part of the '516 Patentee, the Special Master declines to limit the claim scope in the manner proposed by AstraZeneca.

AstraZeneca further relies on the specification of the '516 Patent in support of its position by arguing that the specification "repeatedly describes administering a combination of L-arginine and a statin as 'this invention' or 'the present invention.' " AstraZeneca's Opening Br. at 14. In particular, AstraZeneca asserts that "[c]ontinually referring to an embodiment as 'this invention' or 'the present invention' can establish that the claims only cover that particular embodiment." *Id.* (citing *Honeywell*, 452 F.3d at 1318). However, the facts of the present case do not support AstraZeneca's proposition.

AstraZeneca particularly relies on the following statements in the specification of the '516 Patent to equate the term "invention" exclusively with the "administration of a mixture or combination of L-arginine and a Hmg-CoA reductase inhibitor":

> This *invention* relates generally to a method of treating . . . wherein a substrate of *Nitric Oxide Synthase* ("NOS") and an *agonist of NOS* are *combined* to produce a beneficial effect. '516 Patent col.1 ll.8-13 (emphases added).
>
> It is a further object of this *invention* to provide a *mixture* of *inhibitors of Hmg-CoA reductase* and *biological equivalents of L-arginine* . . . . '516 Patent col.3 ll.41-49 (emphases added).

AstraZeneca asserts that the manner of utilizing the term "invention" within these statements in the '516 Patent is similar to the patent asserted in *Honeywell*. *See* AstraZeneca's Opening Br. at 14; *see also* AstraZeneca's Reply Br. at 6-7, ECF No. 380. While the Special Master agrees that these statements may require a "mixture of combination" of a substrate of Nitric Oxide Synthase (e.g., L-arginine) and an agonist of Nitric Oxide Synthase (e.g., Hmg-CoA reductase inhibitor), these statements do not require the "**administration**" of such a "mixture or combination." Furthermore, the remaining statements within the '516 Patent that refer to mixing

and administering both L-arginine (i.e., a substrate or precursor of Nitric Oxide Synthase) and an Hmg-CoA reductase inhibitor (i.e., an agonist of Nitric Oxide Synthase) in the context of the "invention" are only described as further embodiments. *See* '516 Patent col.3 l.51-col.4 l.35. In this regard, Palmetto has not demonstrated a clear intention to limit the claim scope to require the "**administration**" of a "mixture or combination."

Moreover, the prosecution history and the extrinsic evidence provide ample support for the administration of only an Hmg-CoA reductase inhibitor that is later mixed *in vivo* with L-arginine already present within the body. For instance, Palmetto's expert witness, Dr. John Hallett, states that "a physician would only need to write a prescription for the statin because arginine is already present in patients." Expert Report of John Hallett of June 4, 2014 at 2 ¶ 3, ECF No. 368-10 (hereinafter "June 2014 Hallett Report"). According to Dr. John Hallett, "it was well known to physicians in 1997 that arginine is both produced by the body and obtained from food, and thus is available for bio-transformation for the production of nitric oxide without the need for a special type of arginine supplementation." *Id.* at 2 ¶ 4; *see also* '516 Reexamination File Wrapper, Decl. of Dr. Wayne Kaesemeyer of July 6, 2010 at 2 ¶ 5, PALM0000863, ECF Nos. 229-242 ("L-arginine is naturally present in the circulatory system of humans and . . . can be formed by the human body from other starting materials. Humans also obtain additional L-arginine in their body circulation by eating protein-containing foods . . . . When these proteins are metabolized, L-arginine will be circulating in the bloodstream for uptake by cells, including endothelial cells.").

Even AstraZeneca's own expert, Dr. David Harrison, states that the arginine is "certainly a hundred times higher" in the body, in particular the endothelial cells, than the amount necessary. Dep. Tr. of Dr. David Harrison of June 20, 2014 at 70:5-71:1, ECF No. 380-10

(hereinafter "Harrison Dep. Tr."). In fact, according to Dr. David Harrison, they "have not seen a benefit" when "giving more arginine if there's already plenty in the cell." *Id.* at 71:9-13.

Thus, to the extent that the specification of the '516 Patent references a "mixture or combination of L-arginine and an Hmg-CoA reductase inhibitor," the Special Master finds that such a "mixture or combination" can be created by administering an Hmg-Co-A reductase inhibitor which is thereafter mixed or combined *in vivo* with L-arginine already present in the body.

Therefore, the Special Master construes the phrases "**method for treating**" and "**[such] treatment**" to require the "**administration of a Hmg-CoA reductase inhibitor.**"

II. "subject who would benefit from increased Nitric Oxide production in a tissue" and "subject in need of such treatment"

Palmetto's Proposed Construction	AstraZeneca's Proposed Construction
"the person practicing the method must intend to treat a subject who is at risk for cardiovascular disease conditions and adverse events"	"subject having a recognized need for increased Nitric Oxide production in a tissue" requires intent by the treating medical professional, i.e., "method for treating a nonhyperlipidemic subject with the intentional purpose of increasing nitric oxide production in the subject's tissue"

Palmetto asserts that the preamble of claim 1 in combination with the phrase "subject in need of such treatment" requires that "the person practicing the method must intend to treat a subject who is at risk for cardiovascular disease conditions and adverse events." AstraZeneca asserts that the preamble in combination with the phrase "subject in need of such treatment" requires a "subject having a recognized need for increased Nitric Oxide production in a tissue" and further requires intent by the treating medical professional (i.e., "method for treating a nonhyperlipidemic subject with the intentional purpose of increasing nitric oxide production in the subject's tissue").

Both Palmetto and AstraZeneca cite *Jansen v. Rexall Sundown Inc.*, 342 F.3d 1329 (Fed. Cir. 2003) in support of their respective constructions. Based on the guidance provided in *Jansen*, both parties agree that some level of "intent" is required when practicing the method of claim 1 of the Reexamined '516 Patent. Such an intent element is consistent with the plain and ordinary meaning of the claim. However, the parties disagree as to the focus of the "intent." Thus, we look to *Jansen* to provide guidance for determining this focus.

The patent asserted in *Jansen* involved method claims for "*treating or preventing* macrocytic-megaloblastic anemia in humans . . . which comprises administering . . . *to a human in need thereof*" and for "*treating or preventing* macrocytic-megaloblastic [sic] anemia in humans . . . which comprises orally administering . . . *to a human in need thereof.*" U.S. Patent No. 4,945,083 col.6 ll.20-24, 37-41 (filed Feb. 1, 1989) (emphases added). The *Jansen* court found that "the claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.' " *Jansen*, 342 F.3d at 1333. In particular, the *Jansen* court found that "the recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose." *Id.* (citing *Kropa v. Robie*, 187 F.2d 150, 152 (C.C.P.A. 1951)). In doing so, the *Jansen* court concluded that the combination of the phrases "treating or preventing" and "to a human in need thereof" compel a claim construction requiring the method to be performed for the intentional purposes as stated within the claim. *See id.*

Claim 1 of the Reexamined '516 Patent is nearly parallel to the patent asserted in *Jansen*. The body of claim 1 identifies the target population and requires the method to be performed on a "nonhyperlipidemic subject in need of such treatment." Further, while the preamble identifies the objective as "treating a nonhyperlipidemic subject who would benefit from increased Nitric

Oxide production," the body of claim 1 provides a further objective of "administering . . . to increase Nitric Oxide production in said tissue of the subject." Reexamined '516 Patent col.2 ll. 1-5.

Therefore, the Special Master finds that the focus of the intent is to treat a nonhyperlipidemic subject to increase Nitric Oxide production in the tissue of the subject. In other words, the Hmg-CoA reductase inhibitor must be administered to a nonhyperlipidemic subject with a recognized need for an increase in Nitric Oxide production with the intent to increase Nitric Oxide production. *See, e.g.*, *Jansen*, 342 F.3d at 1334 (The " 'need' must be recognized and appreciated, for otherwise the added phrases do not carry the meaning that the circumstances of their addition suggest that they carry.").

Although this construction is consistent with AstraZeneca's proposed construction, the Special Master does not fully agree with AstraZeneca. AstraZeneca asserts that the disputed phrases "work together to require . . . a specific intent by the treating medical professional." AstraZeneca's Opening Br. at 22. However, the Special Master does not find any support indicating that the intent can only be recognized by a treating medical professional. For instance, the plain language of the claim fails to require this limitation. Moreover, the specification and the prosecution history also fail to require this limitation. There is nothing within the intrinsic evidence requiring the intent to be recognized by a treating medical professional. Hence, the Special Master declines to read such limitation into the claim.

Therefore, the Special Master construes the preamble of reexamined claim 1 along with the phrase "**a subject in need of such treatment**" to mean "**a subject having a recognized need for increased Nitric Oxide production in a tissue**" and require the "**method for treating a nonhyperlipidemic subject who would benefit from increased Nitric Oxide production in**

a tissue" to be **conducted with the intentional purpose of "increasing Nitric Oxide production in said tissue of the subject."**[4]

III. "benefit"

Palmetto's Proposed Construction	AstraZeneca's Proposed Construction
"a reduction of the risk of developing adverse heart and circulatory conditions"	"reducing clinical events"

Palmetto asserts that the term "benefit" means "a reduction of the risk of developing adverse heart and circulatory conditions" while AstraZeneca asserts that the term means "reducing clinical events." While both parties agree that the term "benefit" encompasses a reduction, the disagreement arises as to the object of the reduction.

We first look to the plain language of the claims for determining the object of this reduction. Claim 1 of the Reexamined '516 Patent provides "a method for treating a nonhyperlipidemic subject who would benefit from increased Nitric Oxide production in a tissue." Reexamined '516 Patent col.1 ll.28-30. Even though claim 1 fails to expressly define the term "benefit," dependent claims 15-17 provide some guidance. For instance, claims 15-17 provide that "the treatment reduces the risk" of stroke, angina, and reperfusion injury, respectively, in a subject. Reexamined '516 Patent col.2 ll.17-22.

One of the basic tenets of patent law is that a dependent claim is "construed to incorporate . . . all the limitations of the claim to which it refers," and "then specify a further limitation." 35 U.S.C. § 112(d) (2006). As a result, each dependent claim serves to narrow the scope of the invention in relation to a preceding claim. Therefore, the "benefit" of reexamined

[4] To the extent that Palmetto's arguments rest upon *Jansen's* analysis of the prosecution history, it is unpersuasive. The *Jansen* court stated that the analysis of the prosecution history was supportive of its primary analysis of the ordinary meaning of the claim language. *Jansen*, 342 F.3d at 1332; *see also id.* at 1333 ("Our conclusion as to the meaning of the claims is bolstered by an analysis of the prosecution history.").

claim 1 must encompass the "reduction of a risk" of a specific condition or event identified in dependent claims 15-17. In contrast, AstraZeneca's proposed construction fails to include any benefits encompassing the "reduction of a risk." Completely reading out such "risk reduction" would be inconsistent with the claims and would clearly render dependent claims 15-17 meaningless. Moreover, AstraZeneca's proposed construction would run afoul of 35 U.S.C. § 112(d).

The specification and the prosecution history further support the position that the term "benefit" should encompass a "reduction of a risk." For instance, the '516 Patent provides that the "[s]timulation of NOS . . . may be used to *prevent*, treat, *arrest*, or *ameliorate* any disease or condition which is positively affected by NO production." '516 Patent col.4 ll.60-64 (emphases added). According to Dr. Wayne Kaesemeyer, "prevention in a medical context refers to the *reduction of risk of a clinical event* from occurring." '516 Reexamination File Wrapper, Decl. of Dr. Wayne Kaesemeyer of Oct. 26, 2010 at 4-5 ¶ 9, PALM0012745-46, ECF Nos. 229-242 (hereinafter "Oct. 2010 Kaesemeyer Decl.") (emphasis added).

Dr. Wayne Kaesemeyer further provides that "the '516 Patent teaches the use of statins to treat nonhyperlipidemic subjects who would benefit from increased Nitric Oxide production, and thereby *reduce the risk of clinical events* from occurring." '516 Reexamination File Wrapper, Decl. of Dr. Wayne Kaesemeyer of Nov. 4, 2010 at 8 ¶ 9, PALM0013652, ECF Nos. 229-242 (emphasis added). AstraZeneca maintains that this latter statement confirms its proposed construction. *See* AstraZeneca's Opening Br. at 31. However, the Special Master finds to the contrary. Dr. Wayne Kaesemeyer expressly declares that the benefit is directed to "*reduce the risk* of *clinical events*" without any reference to actually "reducing clinical events."

Tellingly, in the Reexamination Reasons for Patentability/Confirmation, the Examiner acknowledged that "[r]osuvastatin could be used to *reduce the risk*[] [of] cardiovascular death, myocardial infarction, stroke, [arterial] revascularization and angina." '516 Reexamination File Wrapper, Reasons for Patentability/Confirmation of Dec. 7, 2010, PALM0013748, ECF Nos. 229-242 (hereinafter "Reexamination Reasons for Patentability") (emphasis added). Clearly, the specification and the prosecution history are replete with references suggesting that the term "benefit" should encompass a "reduction of a risk."

Even so, AstraZeneca relies on the definition of the term "endpoints" in the specification to support its construction. However, such reliance is unavailing. The '516 Patent only provides that "[t]he term endpoints . . . refers to clinical events." '516 Patent col.2 l.62. The '516 Patent, however, does go on to further state that "[i]t is another object of this invention to achieve a beneficial effect when treating disease conditions . . . and reducing clinical endpoints to include mortality." '516 Patent col.3 ll.34-37. While the "benefit" may encompass "reducing clinical events" as proposed by AstraZeneca, nowhere does the definition of the term "endpoints," much less the remainder of the written description and prosecution history, suggest that the term "benefit" must be limited to only encompassing "reducing clinical events" and therefore reading out "risk reduction." AstraZeneca's proposed construction is not entirely consistent with the specification or the prosecution history.

Therefore, the Special Master finds that the term "benefit" must encompass "reducing the risk of a clinical event" in addition to "reducing a clinical event." Because the prosecution history, in combination with the specification and Palmetto's briefs, is replete with references to "clinical events," the Special Master declines to limit the object of the reduction to only "heart and circulatory conditions," as suggested by Palmetto.

Therefore, the Special Master construes the term "**benefit**" to mean "**a reduction of a clinical event or a reduction of the risk of a clinical event**."

IV. "Nitric Oxide [production]"

Palmetto's Proposed Construction	AstraZeneca's Proposed Construction
"a molecule composed of a nitrogen atom and an oxygen atom"	"nitric oxide produced from the family of enzymes called Nitric Oxide Synthases ('NOS')"

Palmetto asserts that the phrase "Nitric Oxide" should have its customary meaning as a "molecule composed of a nitrogen atom and an oxygen atom." On the other hand, AstraZeneca seeks to further define "Nitric Oxide" as "nitric oxide produced from the family of enzymes called Nitric Oxide Synthases ('NOS')."

Beginning with the plain language, claim 1 of the Reexamined '516 Patent only references Nitric Oxide and does not expressly reference a Nitric Oxide Synthase. In this regard, according to Palmetto, "AstraZeneca's proposed construction seeks to add an extraneous limitation based not on what nitric oxide is, but on how it is 'produced.' " Palmetto's Opening Br. at 21, ECF No. 368. However, "[w]here the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question." *SciMed,* 242 F.3d at 1341. Further, "[t]he patentee may demonstrate intent to deviate from the ordinary and accustomed meaning of a claim term by including in the specification expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Teleflex*, 299 F.3d at 1325. The Special Master finds that these cases comport with AstraZeneca's assertions that "[t]he specification and prosecution history of the '516 Patent teach that nitric oxide production,

as used in the patent, refers to nitric oxide produced by Nitric Oxide Synthases." *See* AstraZeneca's Opening Br. at 34.

"Nitric Oxide" is not explicitly defined by the '516 Patent. Consequently, Palmetto relies on the customary and ordinary meaning of the phrase. While the customary and ordinary meaning of the phrase "Nitric Oxide" may in fact be "a molecule composed of a nitrogen atom and an oxygen atom." However, in the specification, Palmetto clearly indicates that "Nitric Oxide" does not include all forms of Nitric Oxide production thereby suggesting a disavowal of claim scope.

The specification of the '516 Patent repeatedly asserts that the Nitric Oxide disclosed therein is produced from a Nitric Oxide Synthase. As one example, the '516 Patent provides that "a family of enzymes called Nitric Oxide Synthase ('NOS') form nitric oxide from L-arginine." '516 Patent col.1 ll.43-45. This Nitric Oxide Synthase "occurs in many distinct isoforms which include a constitutive form (cNOS)[5] and an inducible form (iNOS)." '516 Patent col.1 ll.50-52. Thereafter, the specification distinguishes the constitutive form and the inducible form of Nitric Oxide Synthase. In fact, the specification even goes so far as to stress the advantages of the constitutive form and the disadvantages of the inducible form of Nitric Oxide Synthase.

For instance, "[t]he constitutive form is present in normal endothelial cells . . . [and] is thought to play an important role in normal blood pressure regulation, prevention of endothelial dysfunction such as hyperlipodemia, arteriosclerosis, thrombosis, and restenosis" while "[t]he inducible form . . . has been found to be present in activated macrophages and is induced in vascular smooth muscle cells, for example, by various cytokines and/or microbial products."

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[5] Like the '516 Patent, this report refers to the constitutive form of Nitric Oxide Synthase (cNOS). However, in the art, it may also be referred to as the endothelial form of Nitric Oxide Synthase (eNOS).

'516 Patent col.1 ll.52-61. In further distinguishing the two forms, the '516 Patent states that "the constitutive form . . . may be active under basal conditions" while "iNOS exhibits negligible activity under basal conditions." '516 Patent col.2 ll.6-9, 30. In fact, "[t]he induced form of the enzyme produces much greater amounts of NO than the constitutive form, and induced NOS appears to be the 'pathophysiological' form of the enzyme because high concentrations of NO produced by iNOS can be toxic to cells." '516 Patent col.2 ll.33-37. The '516 Patent clearly distinguishes the constitutive and inducible forms of Nitric Oxide Synthase.

Because the treatment is directed to diseases related to endothelial dysfunction, it is the constitutive form of Nitric Oxide Synthase that is the focus of the '516 Patent. Notably, the inducible form of the Nitric Oxide Synthase is only discussed in the Description of the Related Art and even so in a disparaging manner. In contrast, the constitutive form of Nitric Oxide Synthase is discussed in the Summary of the Invention and the Detailed Description of the Preferred Embodiments. For instance, in the summary, the '516 Patent provides that "L-arginine as defined herein appears to function as a substrate of cNOS." '516 Patent col.2 ll.66-67. The summary further provides that "another embodiment is a method of stimulating cNOS." '516 Patent col.4 ll.30-32.

Palmetto's very own arguments presented in the reply claim construction brief and during the *Markman* hearing further provide insight as to the meaning of the phrase "Nitric Oxide." For instance, in their reply brief, Palmetto argues that "[b]y asking the Court to construe 'Nitric Oxide' to mean 'nitric oxide produced from the family of enzymes called Nitric Oxide Synthases ("NOS"),' **AstraZeneca seeks to include nitric oxide produced from iNOS in its construction, even though the '516 Patent makes clear that nitric oxide produced from iNOS is 'pathophysiological' and 'toxic to cells.'** [Likewise], AstraZeneca's claim

construction expert – Dr. Harrison – also admitted that the '516 Patent is not directed to nitric oxide produced form iNOS.' " Palmetto's Reply Br. at 9 (emphasis added) (citing Harrison Dep. Tr. at 109:11-25).

Based on the intrinsic evidence, AstraZeneca asserts that the phrase "Nitric Oxide" should be construed to mean "nitric oxide produced from the family of enzymes called Nitric Oxide Synthases ('NOS')" thereby encompassing both the constitutive and inducible forms of Nitric Oxide Synthase. However, the specification of the '516 Patent in conjunction with Palmetto's arguments indicate that the '516 Patent clearly excludes Nitric Oxide produced from the inducible form of Nitric Oxide Synthase as it is toxic to cells. The Special Master finds that such disparaging remarks amount to a disavowal of claim scope thereby signifying that the '516 Patent is only directed to Nitric Oxide produced from the beneficial form of the Nitric Oxide Synthase – the constitutive form. Consequently, the Special Master finds that AstraZeneca's proposed construction does not go far enough.

Therefore, the Special Master finds that the phrase "**Nitric Oxide [production]**" should be construed to mean "**nitric oxide produced from the constitutive form of Nitric Oxide Synthase.**"

V. "increase" and "increased"

Palmetto's Proposed Construction	AstraZeneca's Proposed Construction
Plain and ordinary meaning	"increase[d] by a mechanism of action independent of lowering a subject's cholesterol level"

Palmetto asserts that the terms "increase" and "increased" are well understood in the art and contends that their plain and ordinary meaning governs. AstraZeneca asserts that the terms "increase" and "increased" mean "increase[d] by a mechanism of action independent of lowering a subject's cholesterol level."

The terms "increase" and "increased" in claim 1 of the Reexamined '516 Patent relate to the "Nitric Oxide production." There is nothing inherently ambiguous about these terms as claimed. In fact, notwithstanding AstraZeneca's contentions to the contrary, the Special Master finds that, upon a review of the specification and the prosecution history, the plain and ordinary meaning of the terms "increase" and "increased" would be clear to a person of ordinary skill in the art at the time of the invention, and therefore, no construction is necessary. *See, e.g.*, *Cephalon Inc. v. Mylan Pharm. Inc.*, 962 F. Supp. 2d 688, 700 (D. Del. 2013) (stating that where the "ordinary meaning suffices, construction of the limitation is not necessary"); *cf. O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 521 F.3d 1351, 1361 (Fed. Cir. 2008) ("A determination that a claim term 'needs no construction' or has the 'plain and ordinary meaning' may be inadequate when a term has more than one 'ordinary' meaning or when reliance on a term's 'ordinary' meaning does not resolve the parties' dispute.").

However, to the extent that there is a fundamental dispute over claim scope, AstraZeneca's proposed construction must be rejected as it is unnecessary and unsupported by the intrinsic evidence. The plain language of the claim does not require that any increase is "by a mechanism of action independent of lowering a subject's cholesterol level." Further, such a position is also not supported by the specification or the prosecution history.

It would be erroneous to import such limitations into the plain and unambiguous language of the claim in the absence of any evidence that the '516 Patentee intended to limit the claim scope in such a manner. There is simply no evidence in this case that the '516 Patentee imparted a novel meaning to the terms "increase" and "increased" intending to limit the claim scope as asserted by AstraZeneca.

Therefore, the Special Master finds that the terms "**increase**" and "**increased**" should be

given their **plain and ordinary meaning** and that no construction is necessary.

VI. "nonhyperlipidemic"

Palmetto's Proposed Construction	AstraZeneca's Proposed Construction
"without levels of various lipid types (total cholesterol, LDL and triglycerides) that are too high based on the patient's medical condition and history"	Indefinite; or, alternatively, "having measured lipid levels below the recommended level for consideration of cholesterol-lowering drug treatment"

Palmetto asserts that the term "nonhyperlipidemic" means "without levels of various lipid types (total cholesterol, LDL and triglycerides) that are too high based on the patient's medical condition and history." AstraZeneca asserts that the term "nonhyperlipidemic" is indefinite but proposes in the alternative that the term means "having measured lipid levels below the recommended level for consideration of cholesterol-lowering drug treatment."

First, we address whether the term "nonhyperlipidemic" is indefinite. In the indefiniteness analysis, we must determine whether the term "nonhyperlipidemic," when "read in light of the specification delineating the patent, and the prosecution history, fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *See, e.g.*, *Nautilus*, 134 S. Ct. at 2124.

While the claims of the Reexamined '516 Patent and the specification do not explicitly define the term "nonhyperlipidemic," the prosecution history provides some guidance as to the meaning of this term. For instance, during reexamination, Dr. Wayne Kaesemeyer declared that "[h]yperlipidemia refers to an excessive level of lipids (total cholesterol, LDL, and triglycerides) in the circulatory system." Oct. 2010 Kaesemeyer Decl. at 2 ¶ 4, PALM0012743. In distinguishing those with hyperlipidemia from nonhyperlipidemic subjects, Dr. Wayne Kaesemeyer declared that "a nonhyperlipidemic subject can be selected for treatment to increase Nitric Oxide production, and the resulting effect of the treatment does not depend upon lowering

cholesterol from high levels. A nonhyperlipidemic subject population is very different from the high cholesterol patients (hyperlipidemics)." *Id.* at 2 ¶ 5, PALM0012743. In addition, "[t]he subjects treated according to the '516 Patent may not exhibit outward signs of heart and circulatory conditions, but are at an increased risk for developing more advanced stages of such conditions, and therefore would benefit from increased Nitric Oxide production. Subjects at risk . . . are readily identified by physicians based upon risk factors . . . ." *Id.* at 2-3 ¶ 6, PALM0012743-44.

Dr. Wayne Kaesemeyer clearly distinguished between those subjects who receive statins based on hyperlipidemia (e.g., high cholesterol levels) to reduce cholesterol levels and those subjects who receive statins based on nonhyperlipidemia to increase Nitric Oxide production. It is this latter group that is the focus of the '516 Patent. In other words, subjects not qualified for the traditional statin-based drug therapy for the treatment of hyperlipidemia could instead qualify as the "nonhyperlipidemic" subjects of the Reexamined '516 Patent.

Even the extrinsic evidence suggests that the term "nonhyperlipidemic" has an "ordinary and customary meaning" in the art. For instance, Palmetto's expert, Dr. John Hallett, points out that the medical literature is replete with references to "hyperlipidemia" thereby suggesting that the term "has been commonly used with regard to statins." *See* June 2014 Hallett Report at 11-12 ¶¶ 17-18. Further, Dr. John Hallett states that "physicians understand that subjects who do not have hyperlipidemia are nonhyperlipidemic." *Id.* at 11 ¶ 17. Tellingly, AstraZeneca's own expert, Dr. David Harrison, agrees that "a person of ordinary skill in the art [could] *reasonably conclude* that nonhyperlipidemic means having measured lipid levels below the recommended level for consideration of cholesterol-lowering drug treatment." Harrison Dep. Tr. at 148:2-7 (emphasis added).

Nevertheless, AstraZeneca, relying on its experts, maintains that the term is indefinite because "the lipid levels considered to be high (or 'hyperlipidemic') have changed over the years" and that "the lipid levels that may be deemed too high vary among different populations and from patient to patient." AstraZeneca's Opening Br. at 18 (citations omitted). However, Dr. David Harrison agrees that whether an individual is nonhyperlipidemic "take[s] into account different patient populations such as those with risk factors." Harrison Dep. Tr. at 148:8-15. This suggests that physicians are well-versed in assessing a patient's condition based on their medical history.

The intrinsic evidence and the extrinsic evidence, including the expert testimony, support the position that the specification and prosecution history, in combination with the knowledge of a person of ordinary skill in the art at the time of the invention, convey with reasonable certainty the meaning of the term "nonhyperlipidemic." Accordingly, the Special Master does not find that the term "nonhyperlipidemic" is indefinite. The issue then comes down to the appropriate construction of the term.

Palmetto states that the term "nonhyperlipidemic" requires a reference to a patient's lipid levels based on their medical condition and history while AstraZeneca requires a reference to lipid levels and the recommended levels for consideration of cholesterol-lowering drug treatment.

At the time of the invention, it was already well known in the art to provide statins, such as Hmg-CoA reductase inhibitors. This was even recognized by the '516 Patent. *See* '516 Patent col.1 ll.25-28 (stating that it was known in the art to provide Hmg-CoA reductase inhibitors to "inhibit and reduce the intrinsic biosynthesis of cholesterol in order to reduce the risk factor of hypercholesterolemia and coronary artery death"). In addition, the prosecution

history is replete with references distinguishing the traditional use of statins from that of the '516 Patent. Just as one example, during reexamination, Dr. Wayne Kaesemeyer declared that "the '516 patent provides for the treatment of a subject with a statin in order to provide for increased Nitric Oxide production in a tissue" and that such "mechanism of action differs from the known role of statins in the treatment of high cholesterol." Oct. 2010 Kaesemeyer Decl. at 2 ¶ 4, PALM0012743.

The intrinsic evidence and the extrinsic evidence clearly exclude those subjects receiving statin-based drug therapy for the treatment of hyperlipidemia from the scope of the Reexamined '516 Patent. Therefore, as indicated above and also suggested by Dr. Wayne Kaesemeyer, the Special Master construes the term "**nonhyperlipidemic**" to mean "**having measured lipid levels below the recommended level for consideration of cholesterol-lowering drug treatment.**"

VII. "amount effective"

Palmetto's Proposed Construction	AstraZeneca's Proposed Construction
"the dosage required to increase nitric oxide production so as to provide a benefit"	Indefinite

Palmetto asserts that the phrase "amount effective" means "the dosage required to increase nitric oxide production so as to provide a benefit" while AstraZeneca asserts that the phrase is indefinite.

First, we address whether the phrase "amount effective" is indefinite. In the indefiniteness analysis, we must determine whether the phrase "amount effective," when "read in light of the specification delineating the patent, and the prosecution history, fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *See, e.g.*, *Nautilus*, 134 S. Ct. at 2124; *cf. Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1383-84 (Fed. Cir. 2003) (citation omitted) (The phrase " 'effective amount' is a common and

generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite, provided that a person of ordinary skill in the art could determine the specific amounts without undue experimentation.").

To answer this question, we must first identify the objectives of reexamined claim 1. The plain language of the claim provides "[a] method . . . comprising: administering to the nonhyperlipidemic subject . . . a Hmg-CoA reductase inhibitor in an amount effective to increase Nitric Oxide production in said tissue of the subject." Reexamined '516 Patent col.1 l.28-col.2 l.5. According to the claim, the Hmg-CoA reductase inhibitor is administered in an "amount effective" "to increase Nitric Oxide production in said tissue of the subject." *See also* Section B.II, *supra*. Next in the indefiniteness inquiry, we must determine whether the specification and the prosecution history convey with reasonable certainty the amount of Hmg-CoA reductase inhibitor to be administered for increasing Nitric Oxide production in the tissue of a subject.

First, we note that the plain language of the claims fails to provide any dosage amounts of the Hmg-CoA reductase inhibitor. Therefore, we look to the remaining intrinsic evidence, the specification and the prosecution history, for guidance.

The specification of the '516 Patent discloses dosage information for the Hmg-CoA reductase inhibitor and L-arginine on several instances. For instance, the specification provides that "[a]s part of a 'mixture,' the Hmg-CoA reductase inhibitor is included together with L-arginine [in] clinically effective weight ratios of between 1:2 to 1:150. Even more particularly, the ratio of the Hmg-CoA reductase [to] L[-]arginine in the formulation is between 1:5 to 1:100. [In] [t]he most preferred embodiment of the 'mixture' the ratio of Hmg-CoA reductase inhibitor, most particularly pravastatin, to L-arginine is 1:50." '516 Patent col.6 ll.9-16. The '516 Patent further provides that "[i]n one particular embodiment, the formulation is administered so as to

provide the patient with between 20-40 milligrams per day of the Hmg-CoA reductase inhibitor (i.e., pravastatin) together with a daily dose of L-arginine of between 100 to 200 mg per day. Most preferably, the Hmg-CoA reductase inhibitor, such as lovastatin, is administered at a daily dose of about 20 mg per day together with a dose of about 200 mg per day L-arginine." '516 Patent col.6 ll.35-42.

Based on these disclosures, AstraZeneca asserts that "the only statin amounts identified in the specification are amounts to be administered in combination with L-arginine." AstraZeneca's Opening Br. at 28. However, the intrinsic evidence, including the specification and the prosecution history, in combination with the knowledge of a person of ordinary skill in the art at the time of the invention provides an adequate baseline for determining the amount of Hmg-CoA reductase inhibitor necessary when administered alone to increase Nitric Oxide production.

For instance, during reexamination of the '516 Patent, Dr. Wayne Kaesemeyer declared that "benefits will be observed in nonhyperlipidemic subjects receiving a statin in the FDA approved dosaging, which is commensurate with the dosaging disclosed in the '516 patent." Oct. 2010 Kaesemeyer Decl. at 8 ¶ 18, PALM0012749. In addition, multiple prior art references cited during the reexamination of the '516 Patent also provide dosage levels, albeit for purposes other than increasing nitric oxide, of statins when administered alone that are commensurate in scope with the dosage levels provided in the '516 Patent. *See* Gerard O'Driscoll et al., *Simvastatin, an HMG-Coenzyme A Reductase Inhibitor, Improves Endothelial Function Within 1 Month*, 95 Circulation 1126, 1126 (1997) (administering 20 mg/day of simvastatin to evaluate the effect on endothelium-dependent and endothelium-independent vasodilation and on the response to the inhibitor of nitric oxide synthesis); David Waters et al., *Effects of Monotherapy*

with an HMG-CoA Reductase Inhibitor on the Progression of Coronary Atherosclerosis as Assessed by Serial Quantitative Arteriography. The Canadian Coronary Atherosclerosis Intervention Trial, 89 Circulation 959, 959 (1994) (administering 20 mg/day of lovastatin to study the effect on the evolution of coronary atherosclerosis); David H. Blankenhorn et al., *Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)*, 75 Am. J. Cardiology 455, 455-56 (1995) (administering 10, 20, or 40 mg/day of pravastatin to study the effect on carotid atherosclerosis). Therefore, even though standard dosage levels for the administration of a statin are disclosed, according to Dr. Wayne Kaesemeyer, "[d]osage selection for an individual subject is, of course, left to the physician's judgment." Oct. 2010 Kaesemeyer Decl. at 8 ¶ 18, PALM0012749.

Nonetheless, AstraZeneca asserts that "[t]o the extent the asserted claims are construed to permit administration of a statin alone, the '516 patent contains no guidance for determining what constitutes the amount of a statin administrated to a subject that would be effective to increase nitric oxide production." AstraZeneca's Opening Br. at 28; *see also id.* at 29 (citing Decl. of David G. Harrison of June 6, 2014 at 9 ¶ 26, ECF No. 367-7; Harrison Dep. Tr. at 93:1-18) ("There is no basis, however, for a person of ordinary skill to conclude that the FDA-approved amounts for lowering cholesterol would be effective for increasing nitric oxide production.").

However, even the Examiner, during prosecution of the '516 Patent, stated that "[t]he disclosed 'amount effective to increase endothelial cell nitric oxide synthase activity' in the specification overlaps with the therapeutic dosage range of pravastatin." Jan. 2002 Office Action at 5, PALM0000674. According to the Examiner, "[t]he selection of an optimal mode of administration and an optimal dosing regimen are parameters well within the purview of those

skilled in the art through no more than routine experimentation." '516 Patent File Wrapper, Office Action of July 5, 2000 at 4, PALM0000581, ECF Nos. 229-242; *see also* '516 Patent File Wrapper, Office Action of May 9, 2001 at 4-5, PALM0000647-48, ECF Nos. 229-242 (hereinafter "May 2001 Office Action").

The extrinsic evidence also supports these positions. For instance, Palmetto's expert, Dr. John Hallett, states that "[v]arious statins and statin dosage information are discussed in the '516 patent . . . . These dosages are commensurate with standard dosages for treating patients who have hyperlipidemia." June 2014 Hallett Report at 5 ¶ 6 (internal citations omitted). Dr. John Hallett further states that at the time of the invention, "persons of ordinary skill in the art who prescribed statins were aware of the dosages that had been approved by the FDA, and would look to those dosages when treating a patient." Reply Expert Report of John Hallett of May 22, 2012 at 3 ¶ 8, ECF No. 379-6.

Accordingly, the Special Master finds that, at the time of the invention, the specification and prosecution history convey with reasonable certainty the amount of Hmg-CoA reductase inhibitor effective to increase Nitric Oxide production in the tissue of a subject. The law does not require that a person of ordinary skill in the art determine the effective amount of Hmg-CoA reductase inhibitor with 100% certainty. To the contrary, for a claim to be definite, the "claims, read in light of the specification delineating the patent, and the prosecution history" must inform "with *reasonable certainty*, those skilled in the art about the scope of the invention." *Nautilus*, 134 S.Ct. at 2124 (emphasis added). In fact, "some modicum of uncertainty" is tolerated. *Id.* at 2128 (citation omitted). Hence, the Special Master does not find the phrase "amount effective" as indefinite.

As discussed above, the Special Master finds the phrase "amount effective" to mean "the dosage required to increase nitric oxide production." Therefore, the Special Master does not fully agree with Palmetto's proposed construction. In particular, the Special Master does not find any support within the claims, the specification, or the prosecution history for including the phrase "so as to provide a benefit" within the construction. The plain language of the claim provides a method directed to "treating a nonhyperlipidemic subject who would benefit." Reexamined '516 Patent col.1 ll.28-29. However, such language does not actually require that a benefit is realized. Hence, the Special Master declines to read such limitation into the claim.

Therefore, the Special Master construes the phrase "**amount effective**" to mean "**the dosage required to increase nitric oxide production.**"

VIII. "administering . . . irrespective of the subject's cholesterol level"

Palmetto's Proposed Construction	AstraZeneca's Proposed Construction
Should be construed, if at all, only in the context of invalidity expert reports and dispositive motions pursuant to the Court's scheduling order.	"administering . . . without the intent to alter the subject's cholesterol level"

AstraZeneca asserts that the amendments entered during reexamination improperly broadened the scope of the claims of the '516 Patent. AstraZeneca's Opening Br. at 26-28.

Claim 1 of the '516 Patent claimed:

> A method for treating a subject who would benefit from increased Nitric Oxide production in a tissue comprising:
>
> administering to the subject in need of such treatment, *irrespective of the subject's cholesterol level*, a Hmg-CoA reductase inhibitor in an amount effective to increase Nitric Oxide production in said tissue of the subject.

'516 Patent col.10 ll.18-24 (emphasis added).

Claim 1 of the Reexamined '516 Patent claims:

> A method for treating a *nonhyperlipidemic* subject who would benefit from increased Nitric Oxide production in a tissue comprising:
>
> administering to the *nonhyperlipidemic* subject in need of such treatment a Hmg-CoA reductase inhibitor in an amount effective to increase Nitric Oxide production in said tissue of the subject.

Reexamined '516 Patent col.1 l.28-col.2 l.5. (emphases added).

AstraZeneca asserts that removal of the phrase "irrespective of the subject's cholesterol level" and modification of the subject to provide a "nonhyperlipidemic subject" constitutes improper broadening. For that reason, although the former phrase is not present in claim 1 of the Reexamined '516 Patent, it is nonetheless construed as requested by AstraZeneca in order to determine whether claim 1 was improperly broadened.

AstraZeneca argues that the phrase "administering . . . irrespective of the subject's cholesterol level" should be construed to mean "administering . . . without the intent to alter the subject's cholesterol level" as such meaning "is consistent with the understanding of a person of ordinary skill in the art . . . at the time of the invention." AstraZeneca's Opening Br. at 26. However, the plain language of the claim makes no reference to "altering" or an "intent to alter" a subject's cholesterol level. The construction proposed by AstraZeneca, which seeks to import an intent element, does not comport with the plain language of the claim. Nor do the specification and prosecution history support such a construction.

The Special Master finds that the intrinsic evidence, in particular the prosecution history of the '516 Patent, including that of the reexamination, sheds light on the meaning of the phrase "administering . . . irrespective of the subject's cholesterol level." For instance, during

prosecution of the '516 Patent, the Examiner stated that the phrase "irrespective of the subject's cholesterol level" means "the subject may have *any cholesterol level*." May 2001 Office Action at 6, PALM0000649 (emphasis added).

Such construction was, in essence, confirmed by the Examiner during reexamination of the '516 Patent. For instance, the Examiner stated the following:

> [T]he phrase "irrespective of the subject's cholesterol level" . . . [is] *not limited to the treatment of subjects without hyperlipidemia* . . . . In other words, each and every one of these claims *encompasses treating subjects who have hyperlipidemia* . . . . This fact is evident from the limitation of claim 2 which limits claim 1 to a subject who is non-hyperlipidemic. Therefore, claims 1 and 3-44 clearly encompass treating *subjects who have hyperlipidemia and those that do not have hyperlipidemia*.

Sept. 2010 Office Action at 6, PALM0012609 (emphases added). Even further, in a rejection under 35 U.S.C. § 112, the Examiner stated that the phrase "irrespective of the subject's cholesterol level" is "redundant and unnecessary." *Id.* at 14, PALM0012617. The Examiner suggested that it should be deleted "because [it] is not necessary with the insertion of the phrase 'administering to the nonhyperlipidemic subject.' " '516 Reexamination File Wrapper, Interview Summary of Oct. 7, 2010, PALM0012706, ECF Nos. 229-242. In response, the '516 Patentee acknowledged such redundancy and cancelled the phrase. *See* '516 Reexamination File Wrapper, Amendment of Oct. 28, 2010 at 9, PALM0012729, ECF Nos. 229-242.

Therefore, the Special Master finds the phrase "**administering . . . irrespective of the subject's cholesterol level**" to mean "**administering . . . to subjects who have hyperlipidemia or those that do not have hyperlipidemia**."

The Special Master now turns to whether claim 1 of the '516 Patent was improperly broadened during reexamination. In particular, we must determine whether removal of the phrase "irrespective of the subject's cholesterol level" in conjunction with modifying the subject to provide a "nonhyperlipidemic subject" provides a reexamined claim that includes within its scope any subject matter that would not have infringed the original patent. *See, e.g.*, *Freeman*, 30 F.3d at 1464 (citation omitted) ("A claim is enlarged if it includes within its scope any subject matter that would not have infringed the original patent.").

As suggested by the prosecution history, the scope of claim 1 of the '516 Patent encompassed "subjects who have hyperlipidemia and those that do not have hyperlipidemia." During reexamination, the claim was amended to limit the subjects to only those classified as "nonhyperlipidemic." Therefore, contrary to AstraZeneca's assertions, claim 1 of the '516 Patent was actually further narrowed during reexamination.

The Special Master finds that by restricting the subject to a "nonhyperlipidemic subject," any infringement of claim 1 of the Reexamined '516 Patent would also constitute infringement of claim 1 of the '516 Patent. In this regard, claim 1 of the Reexamined '516 Patent is not broader in scope than claim 1 of the '516 Patent.

Therefore, the Special Master finds that claim 1 of the '516 Patent was not improperly broadened during reexamination.

CONCLUSION

In summary, for the reasons stated herein, the Special Master construes the claim terms at issue as follows:

Claim Term/Phrase	Special Master's Construction
"method for treating" and "[such] treatment"	"administration of a Hmg-CoA reductase inhibitor"
"subject who would benefit from increased Nitric Oxide production in a tissue" and "subject in need of such treatment"	"subject having a recognized need for increased Nitric Oxide production in a tissue" and require the "method for treating a nonhyperlipidemic subject who would benefit from increased Nitric Oxide production in a tissue" to be conducted with the intentional purpose of "increasing Nitric Oxide production in said tissue of the subject"
"benefit"	"a reduction of a clinical event or a reduction of the risk of a clinical event"
"Nitric Oxide [production]"	"nitric oxide produced from the constitutive form of Nitric Oxide Synthase"
"increase" and "increased"	Plain and ordinary meaning
"nonhyperlipidemic"	"having measured lipid levels below the recommended level for consideration of cholesterol-lowering drug treatment"
"amount effective"	"the dosage required to increase nitric oxide production in the tissue of the subject"

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